REMARKS

STATUS OF THE CLAIMS

Claims 1-40 and 42-51 were pending. As shown above, claim 1 has been amended to indicate that the claimed polynucleotides encode a polypeptide that elicits a *Pol*-specific immune response (*see, e.g.,* Example 4). Claim 42 has been canceled, without prejudice or disclaimer. No new matter has been added as a result of these amendments and entry thereof is respectfully requested. The amendments are made to expedite prosecution and are not made for reasons related to patentability. Thus, claims 1-40 and 43-51 are pending as shown above.

CLAIM OBJECTIONS

It was maintained that claim 42 was substantially duplicative of claim 29. Office Action, page 2. Although Applicants note certain differences between the claims, claim 42 has been canceled herein, without prejudice or disclaimer.

35 U.S.C. 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Applicants again submit that the pending claims are fully described by the specification as filed. The Office Action reiterates several points made previously and also makes certain new arguments. Applicants address the Office's arguments below.

A. STRUCTURE/FUNCTION

In the Office Action, it is alleged that the claims do not adequately recite a function of the claimed genus of polynucleotide sequences and, additionally, that the diverse functions of *Pol* proteins (*e.g.,* enzymatic functions of RT and Int) are not correlated with claimed structure. (Office Action, pages 3-4). It appears that this rejection was based, in part, on the Office's definition of the term "HIV Pol polypeptide," which it was alleged that the polypeptide must be identical to one found in an HIV in nature. (Office Action, page 4). Furthermore, it was maintained that the specification "does not disclose how to distinguish between natural amino acid sequences and non-natural sequence that is also at least 90% identical." *Id.*

Because the specification amply describes the structure and function (and correlation between structure and function) of the claimed molecules, Applicants traverse the rejection.

A.I. CLAIM CONSTRUCTION

In a sincere effort to clarify the claimed subject matter, the independent claims have been amended as shown above. By virtue of this amendment, the recitation "an HIV *Pol* polypeptide including an immunogenic HIV *Pol* polypeptide" has been replaced with the term "an HIV *Pol*

polypeptide that elicits a *Pol*-specific immune response." In other words, the function of the polypeptides encoded by the claimed genus of polynucleotides is now more clearly set forth as immunogenic function rather than all biological functions. Of the allegedly numerous and complex functions of naturally occurring *Pol* polypeptides, the pending claims specifically require that the encoded polypeptides must generate a *Pol*-specific immune response.

A.II. STRUCTURE-FUNCTION CORRELATION

Furthermore, Applicants submit that the specification provides ample description regarding the structure/functional relationship between the disclosed polynucleotides sequences and any other sequences that might be embraced by the genus. (Office Action, page 7). Applicants remind the Office that an applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics. (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099, emphasis added).

The specification as filed clearly describes the structure (a reference sequence and variants thereof) and the function (encode an HIV *Pol* polypeptide that elicits a *Pol*-specific immune response) of the claimed biomolecules polynucleotides. Furthermore, the correlation between structure and function is also disclosed -- immunogenic regions of *Pol* were known and could be readily determined. *See, e.g.,* Parker et al. (1994) *J. Immunol.* 152:163-175 and Pogue et al. (1995) *Proc. Nat'l Acad. Sci USA* 92:8166-8170, copies attached hereto. Indeed, it was also known at the time of filing that the correlation between structure and immunogenic function was not as dependent on precise amino acid sequence (structure) as other biological functions such as enzyme activity. In other words, whereas enzyme activity may be destroyed if the amino acid sequence is varied from the wild type, a polypeptide that is used for its immunogenicity can tolerate a variety of substitutions and still induce a specific immune response.

Given the known correlation between *Pol* structure and immunogenic function, it would have been plain to a skilled artisan that Applicants were in possession of the claimed invention at the time the specification was filed, as demonstrated by clear description of structure, function and known correlation between structure and function.

In sum, the structure, the function and the correlation between structure and function of the claimed biomolecules are clearly described in the specification as filed. One of skill in the

art would unambiguously know from this specification that Applicants' were in possession of the claimed polynucleotides at the time of filing.

A.III. POLYPEPTIDES ENCODED BY THE CLAIMED SEQUENCES

The foregoing amendments also fully address the Office's concerns regarding whether the polypeptides encoded by the claimed sequences exhibit "identity" to naturally occurring HIV *Pol* polypeptides. (*See, e.g.,* Office Action, page 4 alleging that the "specification does not disclose ... how to distinguish between natural amino acid sequence and non-natural sequence").

As a threshold matter, Applicants remind the Office that the specification is not required to distinguish between naturally occurring and non-naturally occurring amino acid sequences, regardless of their degree of homology, because the percent homology recitations of the claims are directed to polynucleotides, not proteins. Therefore, the degree of homology of the functional peptide to other peptides is irrelevant to the instant written description inquiry.

In any event, the alleged ambiguity of the recitation "an HIV *Pol* polypeptide including an immunogenic HIV *Pol* polypeptide" has been obviated by these amendments. It is now specified that the claimed polynucleotides must encode a polypeptide that elicits an HIV *Pol*-specific immune response. The non-immunogenic functions of RT and Int are not relevant to pending case. As is well known in the field, biological functions (integrase or transcriptase activity, etc.) of a polypeptide and immunogenic function are separable and, moreover, immunogenic function is typically retained even when amino acid substitutions are made. *See,* Parker and Pogue, above. Thus, the Office's statement, on page 6 that "it is known that a single nucleotide or amino acid change can alter the function of amino acid peptide" is not an accurate reflection of the state of the field, in which it was known that multiple amino acid substitutions could be tolerated in relation to immunogenicity.

The written description requirement is satisfied if the specification reasonably conveys that Applicants were in possession of polynucleotides that encode HIV *Pol* polypeptides that elicit a *Pol*-specific immune response. The specification clearly meets this requirement, as it describes in detail how to make the claimed polynucleotides and determine their ability to generate *Pol*-specific immune responses. *See, e.g.,* Example 4. Thus, it is clear from the specification as filed that the written description requirement is met with respect the claimed molecules.

B. REPRESENTATIVE SPECIES

It was also again asserted by the Office that there were insufficient representative species disclosed in the specification. (Office Action, page 7). In particular, the Office Action asserted

"there is substantial variation between species of immunogenic HIV Pol polypeptides. Therefore, the disclosure of SEQ ID NOs:30-32 does not provide an adequate description of the claimed genus." (Office Action, page 7).

B.I. DISCLOSURE OF A SINGLE SPECIES CAN SATISFY THE WRITTEN DESCRIPTION REQUIREMENT

Applicants remind the Examiner that there is no fixed number of species that must be disclosed to satisfy the written description requirement:

> A "representative number of species" means that the species that are adequately described are representative of the entire genus. ... What constitutes a "representative number" is an inverse function of the skill and knowledge of the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. ... Description of a representative number of species does not require the description be of such specificity that it would provide individual support for each species that the genus embraces. (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099, emphasis added).

Indeed, the Patent Office's "Synopsis of Application of Written Description Guidelines" is clear that a **single** disclosed species may be representative of a "product-by-function" genus when all members exhibit structural identity to a reference compound and when an assay is provided for identifying all variants having the claimed activity:

> **Claim**:
> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A$\longrightarrow$ B.
>
> **Analysis:**
> ... The procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art. ....
>
> There is actual reduction to practice of a single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the reference

sequence, SEQ ID NO:3. The **single species disclosed** is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 U.S.C. § 112, first paragraph as providing adequate written description for the claimed invention. (Example 14, emphasis added.)

Like Example 14, Applicants in the pending case have provided a limit to the structural identity (90% identity), a specified activity of the variants (encode a polypeptide that elicits a *Pol*-specific immune response) and assays for identifying variants exhibiting the specified activity (*e.g., See, e.g.,* page 16, lines 8 to 28 and Example 4 of the specification as well as reference (zur Megede et al. (2003) *J. Virol.* 77:6197-6207, from the laboratory of the present inventors establishing that the expression cassettes encoding subtype B HIV *Pol* polypeptides elicit *Pol*-specific immune responses, submitted previously as Exhibit B). Therefore, even though in no way required to satisfy the written description requirement, Applicants have in fact provided more than one representative species for each claimed "genus."

Actual reduction to practice of a single disclosed species would be more than sufficient to satisfy the written description requirement in the pending case because, as in PTO Example 14, sequences falling within the claimed genus must encode a polypeptide that elicits the specified immune response and must exhibit at least 90% identity to a reference sequence. Here, at least 3 representative species are disclosed. Therefore, as in PTO Example 14, the species disclosed are representative of the genus because all members have at least 90% structural identity with the reference molecule and because of the presence of an assay which applicant provided for identifying all of the at least 90% identical sequences which are capable of eliciting the specified immune response.

B.II. THE RELEVANCE OF PTO EXAMPLE 14

With further regard to Example 14, Applicants note that, during their telephone interview, Examiner's Whiteman and Reynolds indicated that this Example 14 was not relevant because it recites a higher degree of homology than the pending claims and because the reference sequence is a protein sequence rather than a nucleotide sequence, as claimed.

Because Example 14 addresses application of the written description requirement to **all** product-by-function claims, Applicants strongly disagree with this position.

The claim, analysis and conclusion set forth in PTO Example 14 reproduced above are directly relevant and analogous to the written description analysis in the pending case. In particular, the pending claims are analogous to the "product by function" claim presented in PTO Example 14 in that they all recite the at least 90% structural identity to a particularly described sequence include a function limitation (catalytic activity in PTO Example 14 and encoded a polypeptide that elicits a *Pol*-specific immune response in the pending claims). Furthermore, as established by the Patent Office, procedures for making variants of the claimed sequence are utterly conventional in the art and described in the pending application. Also conventional in the art and described in the specification are assays for identifying sequences having the requisite percent identity and the requisite immunogenicity. *See, e.g.*, page 16, lines 8-28 and Example 4 of the specification. The previously submitted reference (zur Megede et al. (2003) *J. Virol.* 77:6197-6207) is also clearly illustrative in demonstrative that the expression cassettes encoding subtype B HIV *Pol* polypeptides elicit *Pol*-specific immune responses.

Applicants now turn specifically to the argument made by Examiners Whiteman and Reynolds that Example 14 may not be relevant to the pending case because the claim at issue recites 90% identity rather than 95% identity. Applicants submit this position raises form over substance and, additionally, defies common sense. Clearly, the number of substitutions encompassed by any given percent identity recitation is a function of sequence length. Therefore, a limitation of 95% identity will result in claims encompassing vastly different numbers of species depending on the length of the reference sequence. For instance, if the reference sequence is 100 residues in length, only 5 substitutions will be tolerated if the genus encompasses only sequences that are 95% identical. If, however, the reference sequence is 6,000 residues in length, sequences having up to 300 substitutions will fall within the scope of the same claims. Notably, Example 14 does not indicate the overall length of the reference sequence. Accordingly, variants exhibiting 95% identity to this reference sequence may include many more substitutions than the variants claimed by Applicants.

The 95% identity set forth in the exemplary claim of Example 14 was not intended to be a "magic" number, which, if a claim did not recite, would automatically be subject to a written description requirement. Such a rule would be an inflexible application of the written description requirement and was clearly not intended by the drafters of Example 14. Rather, the point made in Example 14 (and the other PTO Examples in the "Synopsis of Application of Written Description Guidelines") is that the written description requirement is satisfied with regard to a claimed genus when the claims recite reasonable structural limitations (percent identity) in combination with recitations regarding assayable function.

Furthermore, the position that Example 14 is also not relevant because the reference sequence is amino acid rather than nucleotide is also untenable. Example 14 is clearly applicable to either amino acid or nucleotide sequences. This Example is entitled "product-by-function" not "polypeptide-by-function," a clear indication it was intended to cover any biotechnology claim. Indeed, Examples 6-18 of the PTO publication are all specified as "Biotechnology Examples." Once again, the key point in Example 14 is that satisfaction of the written description requirement in biotechnological arts requires recitation of both structural and functional limitations. In the pending case, like in Example 14, such structural and functional limitations are clearly present.

Accordingly, one of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus, and it is clear that, as concluded in PTO Example 14, the written description of these claims in the pending case provides adequate written description for the claimed invention.

C. THE CITED CASES ARE NOT RELEVANT

In regards to Applicants' previous remarks that *Fiers v. Revel* and *Eli Lilly* were not relevant the Office states, on page 8:

> The argument is not found persuasive because the general concept of the cases is directed to possession of species does not equate with possession of a genus. This is the case here. Thus, the argument is not found persuasive for the reasons set forth above.

Applicants again remind the Office that any written description inquiry is highly fact dependent. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976). Thus, the concept of possession of species versus possession of a genus must be viewed in terms of the particular claims and disclosure.

For the reasons of record and noted above, the fact patterns of *Fiers* and *Eli Lilly* are completely different than those in the case at hand. In *Eli Lilly*, the claims failed to recite any reference sequence whatsoever and, therefore, the genus encompassed by the claims included any polynucleotide encoding insulin. The claims in *Fiers* are similarly broad as they encompass any human DNA encoding fibroblast interferon-beta. By contrast, the genus encompassed by the pending claims is clearly limited to polynucleotides exhibiting 90% homology to a particular reference sequence and which exhibit the recited function.

The holdings of *Fiers* and *Eli Lilly* are not that a genus can never be described by a species, but, instead, that possession of a species can indeed describe possession of a genus if, as

in the pending case, the specification adequately describes the reference sequence as well as the structural and functional limitations of the claimed biomolecules. Again, Applicants' disclosure and claims include both structure and physical properties and, accordingly, the cases cited by the Office are not relevant to case at hand.

D. ADDITIONAL EVIDENCE

With regard to additional evidence of record, including a Rule 132 Declaration, the Office Action states, on page 8:

> Furthermore, the declaration under 37 C.F.R. § 1.132 filed 12/19/02 is insufficient to overcome the rejection of claims 1-40 and 42-47 based upon 112 written description as set forth in the instant Office Action because: for the reasons set forth above the specification does not describe the invention in such as a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For the reasons detailed above, the specification more than amply conveys to the skilled artisan that Applicants were in possession of the claimed invention. Furthermore, as described in Section B.II. above, a single species can be representative depending on the facts. Because the claims are in the general "product-by-function" format and include structural limitations with regard to a reference sequence as well as functional limitations, the three representative species disclosed and claimed are more than sufficient to satisfy the written description requirement.

Even assuming, for the sake of argument only, that the specification were required to identify essential sequences, Applicants submit that such evidence is of record, including the Rule 132 Declarations of record and the evidence submitted herewith. In particular, Applicants' specification identifies (and claims) the *Pol*-encoding sequence, which, at the time of filing were known to include *Pol*-specific epitopes. Possession of the claimed invention is, however, addressed directly in a Declaration filed in September 2003 by Dr. Donnelly. Dr. Donnelly's position is clear that given the facts of this case, Applicants were clearly in possession of claimed molecules at the time of filing.

In view of the foregoing, Applicants submit that the pending claims are fully described by the specification as filed and respectfully request that the rejection be withdrawn.

35 U.S.C. 112, FIRST PARAGRAPH, ENABLEMENT

For the reasons of record, Applicants submit that the specification as filed fully enables

the pending claims. The Office has rejected Applicants' previous arguments for a variety of reasons, addressed below.

A. PERCENT IDENTITY

The central issue regarding enablement remains whether it would require undue experimentation for a skilled artisan to make and use the claimed biomolecules in view of the teachings of the specification. In this regard, it is again maintained that various functions of the Pol protein are unclear and, accordingly, that it would require an undue amount of experimentation for one skilled in the art in view of the prior art to arrive at other sequences that have least 90% sequence identity to the Pol polypeptide encoded by SEQ ID NOs:30-32 and still possess HIV Pol polypeptide activity, particularly enzymatic activity of RT and Int. (Office Action, page 10). In addition, sequence alignments and numerous references are cited in support of the position that the relationship between sequence and function is unclear. (Office Action, pages 11-12).

A.I. FUNCTIONAL LIMITATIONS

Applicants submit that the foregoing amendments clarifying the function and relationship between structure and function obviate the Examiner's concerns. With regard to *Pol* activity, it has always been the case and it now more clearly specified, that enzymatic activity (or lack thereof) of the polypeptides encoded by the claimed polynucleotides is not relevant to the pending claims. Thus, the relationship between tertiary structure and non-immunogenic activities (such as enzymatic activity) is irrelevant. Furthermore, as noted above, it was well known at the time of filing that the immunogenicity was not dependent on precise amino acid sequences.

A.II. PERCENT IDENTITY IS DETERMINED RELATIVE TO POLYNUCLEOTIDE SEQUENCES

Furthermore, the Examiner also errs in setting forth percent identity relative to polypeptides encoded by SEQ ID NOs:30-32. (Office Action, page 10).

First and foremost, percent identity to the reference sequence must be determined relative to the polynucleotide sequence, not the polypeptide sequence. Moreover, the fact that there are a vast number of 819 amino acid peptides (or even as vast number of 819 base pair nucleotide sequences) is of no consequence to the pending claims.

Taken in isolation, the 90% identity limitation requires that a maximum of approximately 245 substitutions in the approximately 2450-long nucleotides of the reference sequences of claim 1. However, the percent identity limitation cannot be taken in isolation, but must be read in

view of the other limitations of the claims. In the pending case, the claims not only clearly recite the reference sequences, they also require that any and all sequences falling within the scope of the claims exhibit the claimed percent identity to those sequences and also exhibit the claimed functionality. The genera are clearly defined by both structure and function.

Applicants also submit that the argument that a broad genus can never be enabled by one (or a few) representative species is legally flawed. It is axiomatic that evidence as to the availability of techniques for discovering additional embodiments to those exemplified in the specification is entirely relevant to the enablement inquiry. (*See, e.g.,* M.P.E.P. § 2164.01 which states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art, citing *United States v. Telectronics Inc.,* 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989)). Routine experimentation is not "undue" and does not establish non-enablement. (see, *e.g., In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988), citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976). In other words, even if the claimed genera were as broad as painted by the Examiner, the test remains whether making and using all the molecules falling within the scope of the claims would require undue experimentation. Here, in view of the clear disclosure regarding structure (homology to a reference sequence) and methods of making and testing polypeptides from these structures, the experimentation is clearly not undue, but merely routine.

A.III. GUIDANCE REGARDING STRUCTURE-FUNCTION CORRELATION

Applicants also strongly dispute the contention that the specification provides no guidance as to which of the nucleotides or amino acids may be changed. *See, e.g.,* Office Action, pages 10 and 13. The specification as filed provides clear examples of substitutions/deletions as claimed, namely SEQ ID NOs:30-32. Furthermore, the additional evidence of record fully supports the specification's teaching that the *Pol* polypeptides were well characterized in terms of immunogenicity and that immunogenicity may be retained when amino acid substitutions are made. *See, e.g.,* Declarations of record, zur Megede et al, as well as Parker and Pogue, attached hereto. Applicants remind the Examiner that the specification does not need to teach in detail (and preferably omits) that which is conventional or well known. *See, e.g., In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The structure and characterization of *Pol* polypeptides was well known at the time of filing, including locations of immunodominant and immunoaccessible regions.

Accordingly, in view of the well-characterized nature of HIV *Pol* proteins and the specification's teachings (*e.g.,* regarding the degree of homology and assaying for *Pol*-specific immune responses), there is ample guidance provided to the skilled artisan regarding the

correlation between structure and function of the claimed biomolecules.

A.IV. GUIDANCE REGARDING FUNCTIONAL ASSESSMENT

Applicants also strongly dispute the Office's contention that "the claimed invention embraces natural sequences and recombinant sequence that could encode a non-functional/functional immunogenic HIV *Pol* polypeptide and the specification does not teach how to determine without further experimentation what sequences are functional." (Office Action, page 13).

The test of enablement is not whether any experimentation would be required, but whether the experimentation would be routine in light of the state of the art and teachings of the specification. Thus, in the pending case, the fact that those working in the field would have understood how to test for immunogenicity and the specification sets forth in detail how to test for antigen-specific immune responses (*e.g.,* Example 4) does not support a finding of nonenablement. The evidence as a whole establishes that testing for *Pol*-specific immune responses was routine at the time of filing.

Further, with regard to the contention that sequences having less than 90% identity but 100% amino acid identity are encompassed by the claims (Office Action, page 14), Applicants again note that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. See MPEP § 2164.08(b). Applicant's claims are limited to polynucleotides exhibiting 90% homology to SEQ ID NOs:30-32 and which encode a polypeptide that elicit a *Pol*-specific immune response. Thus, the claim language itself excludes inoperative embodiments.

Accordingly, in view of the standard assays for determining Pol-specific immune responses as disclosed in the specification, there is ample guidance provided to the skilled artisan regarding determining functional embodiments embraced by the scope of the claims.

B. THE NEWLY CITED REFERENCES DO NOT ESTABLISH UNPREDICTABILITY

The references newly cited by the Office (Baker, Attwood, Gerhold, Russell and Wells) are not germane to the pending case because they all relate to the difficulties in predicting the function of an unknown and uncharacterized polypeptide encoded by a similarly uncharacterized polynucleotide. The pertinent issue in the pending case is whether the specification teaches how to make and use polynucleotides having the requisite homology to the claimed reference sequence that encode a *Pol* polypeptide, wherein the *Pol* polypeptide elicits a *Pol*-specific immune response. This is an entirely different question than whether or not the function of amino acid sequences encoded by polynucleotides identified by genomics methods can be

predicted based on linear sequence alone, as discussed in the cited documents. The HIV *Pol* polypeptide is well characterized in terms of linear structure, tertiary structure, analysis of various domains (including the claimed major homology region) and, moreover, in terms of immunogenicity. Thus, Baker, Attwood, Gerhold, Russel and Wells not relevant to the instant enablement inquiry.

C. THE CASE CITED IS NOT RELEVANT

In regards to Applicants' previous remarks that *Enzo* was not relevant the Office states on pages 15 and 17:

> On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of making and using the claimed genus of polynucleotide sequences, for those skilled in the art to experiment with polynucleotide sequences having 90% identity to the SEQ ID NOs:30-32 and are immunogenic and retain *Pol* activity as intended by the as-filed specification at the time the invention was made. ...
>
> The argument is not found persuasive because Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 teaches that even though the specification is not required to disclose each and every species, there must be sufficient guidance for one skilled in the art to make and use the claimed invention as broadly claimed. This is the case here. In view of the In re Wands factors, the specification does not teach one skilled in the art how to make and use the full scope of the claimed invention.

Applicants reiterate that unpredictability of the claimed invention has not been established and is not supported by the newly cited references. (See, preceding Section B). As noted above, these references relate to predicting function of uncharacterized proteins encoded by uncharacterized polynucleotides. In contrast, the pending claims are directed to well characterized proteins.

Furthermore, the legal determination of enablement is highly fact-specific and rests squarely on a consideration of the record in each particular case. The fact-driven nature of the enablement inquiry is manifest in admonitions by the courts and Board that individual enablement holdings, in isolation, are of limited precedential value, because of the close dependence on the particular facts of each individual case. *See, e.g., In re Angstadt,* 190 USPQ 214 (CCPA 1976); *In re Metcalfe* 161 USPQ 789 (CCPA 1969); *Ex parte Obukowicz,* 27 USPQ2d 1063 (BPAI 1993); *Ex parte Tanksley,* 26 USPQ2d 1384 (BPAI 1992). Accordingly, determining whether the specification satisfied the enablement requirement must be determined in view of the particular claims and disclosure.

For the reasons of record and noted above, *Enzo's* facts are completely different than those in the case at hand. In *Enzo*, the enablement issue was not the breadth of the sequences recited in the claims, but whether the specification enabled the use of these sequences in all cell types.[1] This fact pattern is completely unlike the pending case, in which the Office's central concern is whether the claimed sequences themselves are overly broad. Indeed, the claims in *Enzo* encompassed many more sequences than encompassed by the pending claims. Nevertheless, there was never a question as to enablement of the sequences recited in the claims *per se.* Rather, the enablement inquiry centered around whether the specification enabled in the use of the broadly claimed sequences in any cell type. For a variety of reasons (including failure of others and the lack of the additional data), it was decided on this very narrow issue that the specification was not enabling.

Thus, because the holding in *Enzo* does not relate to the question of enablement of sequences, it is irrelevant. Indeed, the fact that the court in *Enzo* did not question the enablement of an extremely broad genus of sequences (*i.e.,* any DNA sequence comprising a segment of any gene that, when transcribed into RNA, regulated the function of the gene), actually supports Applicants' argument that their specification fully enables claims that encompass only sequences exhibiting the requisite high level of homology to a reference sequence and the recited function.

D. ADDITIONAL EVIDENCE

With regard to additional evidence of record, including a Rule 132 Declaration, the Office Action states, on page 15:

> The declaration under 37 C.F.R. § 1.132 filed 9/8/03 is insufficient to overcome the rejection of claims 1-40 and 42-47 based upon 112 enablement as set forth in the instant Office Action because: in view of the In re Wands factors, the as-filed specification does not provide sufficient guidance and/or factual evidence for one skilled in the art to make and/or use the full scope of the claimed invention.

Similarly, the Examiner dismisses zur Megede et al. on the grounds that it is related to type B sequence not type C and does not indicate how the methods are applicable to the claimed polynucleotides. (Office Action, pages 15-16).

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[1] A representative construct claim in *Enzo* reads as follows A non-native DNA construct which, when present in a prokaryotic or eukaryotic cell containing a gene, produced an RNA which regulates the function of aid gene, said DNA construct containing the following operably linked DNA segments: (a) a transcriptional promoter sequence; (b) a transcription termination sequence; and (c) a DNA segment comprising a segment of said gene, said gene segment located between said promoter segment and said termination segment, whereby the RNA produced by transcription of the inverted gene segment regulates the function of said gene.

As detailed above, the variation and relationship as between various sequences has been clarified by amendment herein. Furthermore, such variation is not relevant to the enablement inquiry. Applicants have clearly provided evidence regarding all eight *Wands* factors, demonstrating that (1) the experimentation required to align sequences, make constructs and test those constructs for their ability to elicit a *Pol*-specific immune response was routine (*see, e.g.,* Donnelly Declaration); (2) the amount of direction provided in regards to all aspects of (1) is significant; (3) working examples are present; (4) the nature of the invention is a product-by-function; (5) the state of the field was such that making and using the constructs would have been routine; (6) the high level of skill in the art; (7) the predictability of the field in terms of determining percent identity and the high level of knowledge regarding structure of *Pol* polypeptides and their immunogenicity (along with the irrelevance of enzymatic activity); and (8) the fact that the claims are limited by structure, by function, and by the known relationship between *Pol* sequence and immunogenic function.

The Office must consider evidence provided by the applicant that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *See, e.g.,* PTO Training Manuals on Enablement, page 42; MPEP 716.09; *In re Brandstadter,* 179 USPQ 286 (CCPA 1973); *In re Ambruster,* 185 USPQ 152 (CCPA 1975); and *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). The evidence provided by the applicant need not be conclusive but merely convincing to one skilled in the art. PTO Training Manual on Enablement, page 42.

The evidence of record in the pending case (including Declaration evidence and publication by zur Megede et al.) clearly establishes that it would not require undue experimentation to make and use the claimed subject matter. At the time of filing, determining sequence identity and testing for *Pol*-specific immune responses were both utterly routine. The specification also provides guidance (*e.g.,* Example 1 of the specification) regarding selection and modification of native *Pol* HIV sequences. Substantial guidance is also given in regards to determining whether a *Pol* polypeptide is expressed from the claimed expression cassettes and whether this polypeptide elicits a *Pol*-specific immune response, as required by the claims. (See, *e.g.,* Examples and attached Declaration and reference by zur Megede et al.). Again, the guidance regarding the effect of amino acid substitutions on *Pol* enzymatic activity is entirely irrelevant to any enablement inquiry. The relevant inquiry is whether the specification teaches how to make and use *Pol* encoding polynucleotides as claimed that elicit a *Pol*-specific immune response.

Indeed, the relevance of zur Megede is clearly evident to all aspects of the claimed subject matter. Indeed, by summarily dismissing Dr. Donnelly's statement that the findings and methods of zur Megede et al. are applicable to modified polynucleotides encoding subtype C *Pol*

proteins, the Examiner is improperly substituting personal knowledge for that of Dr. Donnelly. When a rejection is based on facts within the personal knowledge of the Examiner, the data relied upon should be stated as specifically as possible, and the reference must be supported, when called for by the applicant, by an affidavit from the Examiner. 37 C.F.R. 1.104(d)(2); MPEP 2144.03. Applicants therefore request that the Examiner support the position that results relating to subtype B are inapplicable to analogous constructs obtained from subtype C strains.

In view of the working examples and clear teachings of the specification, including actual sequences and teachings regarding how to determine percent identity as between polynucleotides, prepare and administer expression cassettes comprising polynucleotides, express proteins from these expression cassettes and test those proteins for immunogenicity, Applicants submit that a *prima facie* case of non-enablement has not been (and indeed cannot be) established. Accordingly, withdrawal of this rejection is respectfully requested.

PROVISIONAL DOUBLE PATENTING

Applicants request the provisional double patenting rejection be held in abeyance until indication as at allowable claims is received in one of the applications.

CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §1.16, §1.17, and §1.21, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648, referencing Atty. Docket No. 2302-1631.20.

Please direct all further written communications regarding this application to:

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